Remarks

Reconsideration of this Application is respectfully requested. Pursuant to 37 C.F.R. § 1.116(a), Applicants respectfully request entry of this Amendment and Reply after a Final Office Action because it is accompanied by a Request for Continued Examination in compliance with 37 C.F.R. § 1.114.

Upon entry of the foregoing amendments, claims 62-77 are pending in the application, with claim 62 being the independent claim. Claims 1-61 were previously cancelled without prejudice to or disclaimer of the subject matter therein.

Claim 62 is sought to be amended to clarify that the topical administration is directly to the eye of the patient. Support for the amendment of claim 62 can be found, for example, at page 24, lines 27-30 of the specification. Claim 65 is sought to be amended to correct a typographical error.

New claims 66-77, which depend directly or indirectly from claim 62, are sought to be added to claim additional embodiments of claim 62. Support for new claims 66-68 can be found, for example, at page 20, lines 13-23 of the specification. Support for new claims 69-72 can be found, for example, at page 24, line 27 to page 25, line 18. Support for new claim 73 can be found, for example, at pages 24-25, Example 8 and pages 21-22, Example 2. Support for new claim 74 can be found, for example, at pages 24-25, Example 8 and page 22, Example 3. Support for new claim 75 can be found, for example, at pages 24-25, Example 8 and pages 22-23, Example 4. Support for new claim 76 can be found, for example, at page 19, lines 19-30. Support for new claim 77 can be found, for example, at page 20, lines 1-12.

As such, these changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 103

A. Claims 62, 64 and 65

The Examiner rejected claims 62, 64 and 65 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke (US 2001/0021380) in view of Fabrizio *et al.* (EP 0 492 448 A1), Horwitz (WO 92/22324), Adair *et al.* (EP 0 516 785 B1), and Reza Dana (WO 00/27421). *See* Office Action at pages 2-5. Applicants respectfully disagree for at least the reasons of record. However, solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 62 to clarify that the topical administration is directly to the eye of the patient and have added new claims 66-77. Applicants will address the Examiner's rejection in the event the Examiner finds it applicable to the present claims.

1. Legal Principles

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. § 2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v.*

Teleflex Inc., 127 S.Ct. 1727 (2007). The Office has published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc.,* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), and M.P.E.P. § 2143. Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were predictable. *Id., e.g.,* at 57529.

> ***2. One of ordinary skill would have considered the ability of antibody fragments to penetrate the cornea differently than the ability to penetrate other tissues, such as tumor tissue, because of the physiological differences between the cornea and other tissues.***

At page 3 of the Office Action, the Examiner alleges that Applicants have not provided:

> sound scientific reasoning or objective evidence *why* one of ordinary skill in the art would have considered the ability of an $F(ab')_2$ antibody to penetrate the cornea any different than the ability of an $F(ab')_2$ antibody to penetrate any other tissue, e.g., tumor tissue.

(emphasis in original).

Applicants assert that such evidence is available, as discussed in the Amendment and Reply filed on February 17, 2009 and for the additional reasons that follow. The cornea is the front part of the eye that covers the iris, pupil and anterior chamber. *See, e.g.,* page 7 of the Amendment and Reply filed on February 17, 2009. The cornea contains five specialized layers, including Bowman's layer and Descemet's membrane,

two barrier layers containing collagen. *See id.* Unlike many other types of tissues, the cornea does not contain blood vessels. *See, e.g.,* Zhu *et al.,* J. Interferon Cytokine Res. 19:661-669; 1999 at page 661 (document NPL31 of the Information Disclosure Statement dated March 16, 2007; copy attached as Exhibit A). In view of the lack of lack of blood flow and barrier layers associated with the corneal structure, one of ordinary skill in the art would understand that systemically administered drugs would have poor access to the cornea. *See, e.g.*, Sasaki, H., *et al.*, Crit. Rev. Ther. Drug Carrier Syst., 16:85-146; 1999 (Abstract attached as Exhibit B).

Topical administration can be an alterative to systemic administration. However, one of skill in the art would have understood at the time the present application was filed that the cornea is an effective barrier to topical penetration, because the corneal epithelium has annular tight junctions which surround the corneal epithelium. *See id.* Additionally, one of ordinary skill would have understood that topically applied drugs are rapidly eliminated from the pre-corneal area. *See id.*

In addition, Applicants assert that one of ordinary skill in the art would have understood at the time the present application was filed that the penetration of therapeutic agents into tumor tissue is different than the penetration of therapeutic agents into non-tumor tissue (*e.g.,* cornea tissue) because of the differences between tumor physiology compared to normal tissue. Tumor physiology has significant influence on the sensitivity to anti-cancer drugs, including antibodies. *See, e.g.*, Tannock, I.F., Cancer Metastasis Rev., 20:123-132, 2001 (Abstract enclosed as Exhibit C); Jain, R.K., Cancer Metastasis Rev. 9:253-266, 1990 (Abstract enclosed as Exhibit D); and Jain R.K., Annu. Rev. Biomed. Eng. 1:241-263, 1999 (Abstract enclosed as Exhibit E). Tumors have

heterogeneous blood supply or poorly vascularized, elevated interstitial pressure, and large transport distances in the interstitium, resulting in a non-uniform uptake of agents. As such, one of ordinary skill in the art would have considered the ability of a $F(ab')_2$ antibody to penetrate the cornea differently than the ability of a $F(ab')_2$ antibody because of the differences in tumor physiology compared to non-tumor tissue. Thus, one of ordinary skill in the art would not have necessarily expected that the improved penetration of $F(ab')_2$ fragments into tumor tissue disclosed in Horwitz would apply to the penetration of $F(ab')_2$ fragments into non-tumor tissues such as cornea tissue.

Thus, one of ordinary skill at the time the present application was filed would have understood the ability of therapeutic agents, such as antibody fragments, to penetrate the cornea differently than the ability of agents to penetrate other tissues such as tumor tissue, because of the physiological and structural barriers of the cornea to the systemic and topical administration of agents. Accordingly, Applicants maintain that it was not predictable that $F(ab')_2$ antibody fragments would better penetrate the cornea even if the fragments might better penetrate other tissues such as tumor tissue.

For at least these reasons, Applicants maintain that the Examiner has not met the criteria required to establish a *prima facie* case of obviousness of claim 62. Claims 64 and 65 depend indirectly and directly on claim 62, respectively. Applicants submit that claims 64 and 65 are allowable for at least the same reasons set forth above regarding claim 62, and further in view of their own respective distinguishing features. *See* M.P.E.P. § 2143.03, citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) ("If an independent claim is nonobvious under 35 U.S.C. § 103, then any dependent claim depending therefore is nonobvious.").

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 62, 64 and 65.

3. Even if prima facie obviousness were established, evidence of unexpected results exists which would overcome such a rejection.

Secondary considerations of non-obviousness include unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 694, 148 U.S.P.Q. 459, 467 (1966). The Federal Circuit has recently reaffirmed that the USPTO must in all cases consider any evidence tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345 (Fed. Cir. 2007). As discussed above, the Examiner has not established a *prima facie* case of obviousness with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected and superior properties of the claimed subject matter.

As evidence in support of the non-obviousness of the claimed subject matter, Applicants provide the attached Declaration of Dr. Jorge F. Paniagua-Solís as Exhibit F, along with additional description of the methodology of Exhibit F attached. In particular, Exhibit F provides data showing that treatment with anti-TNFα $F(ab')_2$ fragments significantly and unexpectedly increases graft cornea survival (*see* Figure 1) and decreases the morphological properties of the cornea associated with graft rejection (*see* Figure 2). Furthermore, it is Dr. Paniagua-Solís' opinion that the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner. *See, e.g.*, paragraph 11.

Therefore, even if a prima facie case of obviousness were established, which it has not, Applicants respectfully contend that these unexpected results would be sufficient to overcome such a rejection.

B. Claim 63

The Examiner also rejected claim 63 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke in view of Fabrizio *et al.*, Horwitz, Adair *et al.*, Looareeswan *et al.* (Am. J. Trop Med. Hyg. 61:26-33, 1999) and Reza Dana. *See* Office Action at pages 5-7. Claim 63 depends from claim 62. Thus, Applicants assert that claim 63 is also allowable for at least the reasons set forth above regarding claim 62, and respectfully request reconsideration and withdrawal of the rejection.

C. New Claims 66-77

New claims 66-77 depend either directly or indirectly from claim 62. Thus, Applicants assert that claims 66-77 are allowable for at least the reasons set forth above regarding claim 62, and further in view of their own respective distinguishing features. *See* M.P.E.P. § 2143.03, citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) ("If an independent claim is nonobvious under 35 U.S.C. § 103, then any dependent claim depending therefore is nonobvious."). In particular, the combination of the cited references does not teach topical administration of anti-TNFα $F(ab')_2$ neutralizing antibody fragments directly to the eye for the treatment of corneal transplant within 24 hours, 2 hours or 30 minutes following corneal transplant (claims 66-68); administration at least 3 times a day, or about every 10 to 12 hours, for about 8 weeks (claims 69 and 70); or the compositions specified in claims 73-77.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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